Conclusions: In a heterogeneous population referred for chest pain, DASS provides useful, independent prognostic information, according to the imaging pattern and extent and severity of perfusion abnormalities.

914-97 Prediction of Severe Coronary Artery Disease With Tc-99m Sestamibi Perfusion and Function Studies: A Comparison With Clinical History, Physical Examination, and Electrocardiographic Data

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Simultaneous perfusion and function studies were obtained in 167 patients with cardiac catheterization ≤ 90 days; 76% were men, mean age 60 years. Multivariable logistic regression analysis was used to identify independent predictors of the 54 patients with severe, multivessel coronary artery disease. Composite clinical history, physical examination, and rest electrocardiographic variables were combined in the form of a clinical index for creating baseline risk adjustment. Multivariable logistic regression modeling was performed including important univariable predictors ($p < 0.20$) of multivessel coronary artery disease with exercise electrocardiographic, perfusion, and function variables. The final model included:

Multivariable Model	Coefficient (s.e.)	chi^2	p value
Peak Ejection Fraction ≤ 50%	−0.06 (0.02)	7.8	0.005
Number Reversible defects	0.42 (0.21)	4.3	0.039
Number of defects	0.55 (0.28)	3.8	0.05
ST depression (millimeters)	0.89 (0.26)	11.8	0.0006
Clinical History Index	0.60 (0.17)	12.2	< 0.001

Conclusion: Simultaneous myocardial perfusion and function studies with Tc-99m sestamibi are able to improve prediction of the extent of coronary disease, even when clinical history and electrocardiographic data are also available.

914-98 Prognostic Value of Resting Thallium-201 Imaging: Measurement of Infarction but Not Ischemia Predicts Outcome

Todd D. Miller, Timothy F. Christian, David O. Hodge, Andre C. Lapeyre, Brian P. Mullan, Raymond J. Gibbons. *Mayo Clinic, Rochester, MN*

The purpose of this study was to examine the prognostic value of resting thallium-201 scintigraphy. Two hundred fifty-one patients (178 M, 73 F, age 66 ± 10 years) who underwent resting tomographic thallium-201 imaging were followed for a median duration of 25 months. There were 54 initial cardiac deaths or myocardial infarctions and 97 total deaths. Thallium uptake was graded on early and 4 to 6 hour delayed images by 2 experienced observers in 14 short axis segments using a 5-point scale. Five variables were analyzed for association with outcome: extent of redistribution, extent and severity of redistribution, extent of defect on the delayed image (DEFECT DELAYED), extent and severity of DEFECT DELAYED, and increased lung uptake. Results of the Cox univariate analysis for the endpoint cardiac death or myocardial infarction were:

Variable	χ^2	p
Extent of redistribution	< 1	NS
Extent and severity of redistribution	< 1	NS
Extent of DEFECT DELAYED	4.3	0.04
Extent and severity of DEFECT DELAYED	5.2	0.02
Increased lung uptake	5.1	0.02

In the Cox multivariate analysis, the only variable independently associated with outcome was extent and severity of DEFECT DELAYED. In the subset of 88 patients who additionally underwent 24 hour delayed imaging, neither extent of redistribution nor extent and severity of redistribution was predictive of outcome. For the endpoint total mortality, the only variable associated with outcome was the extent and severity of DEFECT DELAYED (univariate χ^2 = 4.1, p = 0.04).

Conclusion: Measurement of DEFECT DELAYED ("infarction") but not measurement of redistribution (resting ischemia) predicts outcome in patients undergoing resting thallium imaging.

914-99 Is ST Segment Depression During Pharmacologic Stress Testing a Predictor of Events?

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The relationship between ST depression during pharmacologically-induced coronary hyperemia and prognosis may differ from that during exercise. This study examined the relation between ST depression during adenosine-SPECT thallium imaging and prognosis in 233 patients (pts) with angiographic evidence of coronary artery disease (CAD, ≥ 50% diameter stenosis of 1 or more vessels). During a mean follow-up of 31 ± 20 months there were 32 events (cardiac death or nonfatal myocardial infarction). ST segment depression was present in 38 pts and absent in 195 pts. There were 27 events in pts with no ST depression (14%) and 5 events in pts with ST depression (13%, P:NS). Actuarial life table analysis showed no difference in event-free survival in pts with and without ST depression. By multivariate Cox survival analysis the important predictor of events was the size of perfusion abnormality ($P < 0.05$). The 5 pts with ST depression and events differed from the pts with ST depression and no events in the number of vessels diseased (2.1 ± 0.7 vs 3.0 ± 0.1, P = 0.01). Thus, ST depression during adenosine SPECT thallium imaging in pts with documented CAD is not a risk factor of events. This may be due to the dual role of collaterals in relation to ST depression and cardioprotection.

914-100 Are Hemodynamic Changes During Adenosine Infusion Predictive of the Diagnostic Accuracy of Adenosine Sestamibi SPECT?

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Whether adenosine myocardial perfusion SPECT remains accurate for detecting CAD in the absence of peripheral hemodynamic changes is controversial. To assess the hemodynamic correlates of perfusion defects, we studied 222 consecutive patients (age 71 ± 11 years) without prior MI or revascularization who underwent dual isotope myocardial perfusion SPECT (DIMPS) (rest Tl-201/adenosine sestamibi) and catheterization ≤ 6 months of DIMPS. Visual analysis used 20 SPECT segments and a 5 point scoring system (0 = normal, 4 = absent uptake). The SPECT study was considered abnormal if ≥ 2 segments had a stress score of ≥ 2 or ≥ 1 segment had a stress score of ≥ 3. The overall sensitivity, specificity and accuracy of adenosine DIMPS for detecting CAD (≥ 50% stenosis) were 94% (173/183), 74% (29/39) and 91% (202/222), respectively. The diagnostic value of DIMPS based on hemodynamic changes (heart rate = HR; systolic blood pressure = SBP) were as follows:

Patient category	Sensitivity	Specificity	Accuracy
HR↑ ≤ 10bpm	95% (107/112)	68% (15/22)	91% (122/134)
HR↑ > 10 bpm	93% (66/71)	82% (14/17)	93% (82/88)
SBP↓ ≤ 10 mmHg	94% (63/67)	75% (9/12)	91% (72/79)
SBP ↓ > 10 mmHg	95% (110/116)	74% (20/27)	91% (130/143)
HR↑ ≤ 10bpm and SBP↓ ≤ 10 mmHg	94% (45/48)	57% (4/7)	89% (49/55)
HR↑ > 10 bpm or SBP↓ > 10 mmHg	95% (128/135)	78% (25/32)	92% (153/167)

p = ns between each category.

The prevalence of left main or multivessel CAD and extent of scan abnormality were similar among all groups. Thus, the diagnostic accuracy of adenosine DIMPS is high even in patients without hemodynamic evidence of adenosine effect.

915 Basic Coronary Vascular Physiology/Studies During Ischemia

Monday, March 25, 1996, Noon–2:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: Noon–1:00 p.m.

915-84 Loss of Nitric Oxide Synthase Activity in the Post-Ischemic Heart: Evidence for Acidosis Induced Enzyme Denaturation

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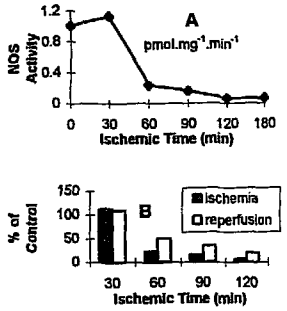
Endothelium-dependent vasodilation is impaired during ischemia and reperfusion, and this may be due to altered nitric oxide (NO) generation from nitric oxide synthase (NOS). However, the time course of NOS activity alterations within ischemic and reperfused myocardium and the contribution of ischemia and reperfusion-induced pH changes to these alterations are not known. Therefore, NOS activity and myocardial pH were measured in isolated rat hearts subjected to 30 to 180 min of global 37º C ischemia or ischemia followed by 45 min reperfusion, using a new sensitive and specific assay of arginine conversion to citrulline with partial purification of the enzyme, and ^{31}P NMR, respectively. While NOS activity was largely unchanged during the first 30 min of ischemia a subsequent large progressive decrease occurred

with complete loss of activity by 120 min (fig A). During reperfusion a partial two fold recovery of NOS activity was noted after 60 or 90 min of ischemia but not after more than 120 min of ischemia (fig B). During ischemic durations greater than 30 min intramyocardial pH fell asymptotic to a value of 5.5. When purified constitutive NOS was subjected to pH 5.5 enzyme activity was similarly lost and only partially restored with restoration of the pH to values of 7.4.



These data suggest that ischemia and reperfusion-induced pH changes could account for the loss of activity seen during ischemia and the partial return observed on reperfusion. The loss of NOS activity observed during ischemia may contribute to the loss of endothelial dependent vasodilation in the post-ischemic heart.

915-85 Expression of Cell Adhesion Molecules in Human Arteriosclerosis

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The interactions between cell adhesion molecules and components of the extracellular matrix are often discussed in relation to their ability to modulate the proliferative, migratory and apoptotic processes involved in plaque formation. Therefore, we assessed the expression of several integrin subunits and gpIV (thrombospondin receptor) by the analysis of coronary and peripheral arteriosclerotic tissue from 22 patients, using immunoperoxidase staining with monoclonal antibodies (Immunotech). Morphometric results are presented as means ± SD of positive/total cells found in ten different intimal areas/lesion. The data are as follows:

Cell adhesion protein	Positive cells/mm²	Total cells/mm²	Expression (%)
α_2 (CD49b)	9 ± 16	436 ± 324	2
α_3 (CD49c)	92 ± 89	431 ± 289	21
α_5 (CD49e)	29 ± 38	418 ± 309	7
α_6 (CD49f)	0	406 ± 318	0
α_v (CD51)	198 ± 237	393 ± 268	50
β_1 (CD29)	348 ± 259	391 ± 268	89
β_3 (CD61)	58 ± 87	349 ± 283	17
gpIV (CD36)	211 ± 244	387 ± 271	54

Smooth muscle cells are the predominant intimal cell type and frequently display distinct signals of α_3, α_v, β_1, β_3 and gpIV cell surface receptors. Only sparse immunoreaction was detected for the integrins α_2 and α_5, and none for α_6. Interestingly, positive correlations were found between the intimal cell density and the expression of α_3, α_v, β_1 subunits and of gpIV ($r > 0.70$; $p < 0.01$). Five lesions expressed high levels (> 80%) of α_3, α_v and β_1 integrins in adjacent medial areas.

In summary, our study demonstrates distinct expression patterns of specific integrin subunits and of gpIV in human arteriosclerotic lesions. Cell adhesion proteins may be attractive targets of cell-directed, therapeutic approaches, the ultimate goal being the mitigation of plaque growth, possibly by modulating cellular anchorage and inducing apoptosis.

915-86 Time Course of PECAM-1, ICAM-1, and E-Selectin Expression in Response to TNF-α Stimulation in Human Coronary Artery Endothelial Cells

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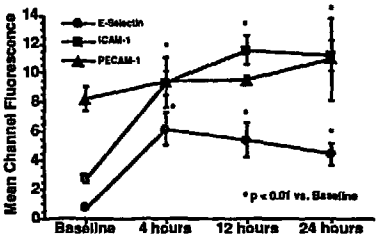
Leukocyte-endothelial cell adhesion molecules (CAMs) have been implicated in the pathogenesis of myocardial ischemia-reperfusion and coronary artery restenosis in animal models. Accordingly, we investigated the time course of TNF-α induced expression of ICAM-1, E-selectin, and PECAM-1 on human coronary artery endothelial cells (HCAECs). HCAECs were grown to confluence and treated with rhTNF-α (10 ng/ml) for 0, 4, 12, or 24 hrs (n = 6–8/group) and analyzed using indirect immunofluoresence techniques. Monoclonal antibodies against ICAM-1 (RR 1/1, Boehringer Ingelheim), E-selectin (CY1787, Cytel), and PECAM-1 (WM59, BioDesign) were utilized to determine the relative expression of these CAMs at the specified time intervals. These data demonstrate that ICAM-1 and E-selectin expression can be upregulated on HCAECs by rhTNF-α at 4, 12, and 24 hrs following cytokine stimulation. PECAM-1, however, is constitutively expressed at extremely high levels, and appears to be unaffected by rhTNF-α stimulation. We conclude that CAMs are expressed on human coronary artery endothelial cells, and the degree of expression is markedly increased by rhTNF-α stimulation.



Furthermore, these CAMs may play an important role in the pathogenesis of coronary artery disease in humans.

915-87 A Single Intracoronary Bolus of Basic Fibroblast Growth Factor Increases Myocardial Perfusion Bed in a Porcine Model of Chronic Ischaemia

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Basic fibroblast growth factor (bFGF) is a polypeptide that induces endothelial cell and smooth muscle cell proliferation. We studied its effects in reducing the ischaemic burden in a porcine coil stenosis model. *Methods* A stenotic lesion was created in the right coronary artery (RCA) in 9 juvenile Yorkshire pigs using a balloon delivered copper-gold coil. In 3 additional control pigs no coil was delivered. At 28 ± 5 days later, the RCA stenosis was confirmed by angiography and the RCA perfusion bed was quantified with contrast echocardiography (CE) using a selective injection of sonicated albumin into the RCA. Animals were then allocated to receive either a single bolus of 100 mcg of bFGF (n = 7) or NAP04 buffer vehicle (n = 5) delivered into the left coronary artery. Repeat CE was performed 14 days later. Total myocardial and RCA perfusion beds were obtained by blinded analysis of the short axis images. The RCA perfusion bed size was expressed as a percent of the total perfusion bed and the percent change between studies was calculated. *Results* The mean diameter stenosis at the coil was 83.3 ± 18.7% and was no different in the bFGF and vehicle pigs. In those animals with a stenosis who received bFGF the RCA perfusion bed increased by 13.2 ± 4.3% whereas in the animals who received vehicle it decreased by 7.5 ± 3.9% ($p = 0.014$). No increase in perfusion bed occurred in those pigs without a coil. *Conclusion* In the presence of a coronary stenosis, a single bolus of bFGF delivered into the contralateral artery improves perfusion in the stenotic vessel's territory.

915-88 Cell — Cell Interactions in the Development of Atherosclerosis: Macrophage Conditioned Media Stimulates Vascular Smooth Muscle Cell Proliferation and Matrix Production

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Matrix protein production and vascular smooth muscle cell proliferation are the hallmarks of atherosclerosis. Cell-cell interactions are important in the regulation of proliferation and protein synthesis. We tested the interaction between macrophages, a prominent cell in the injury-response of coronary arteries, and vascular smooth muscle cells (VSMC) obtained from porcine coronary arteries. The purpose of this study was to examine the effects of macrophage conditioned media on proliferation and the expression of osteopontin, an Arg-Gly-Asp-containing acidic phosphoprotein in vascular smooth muscle cells. Osteopontin is present in atherosclerotic plaques and is necessary for calcification associated with vascular disease. Macrophage conditioned media at 1:4 dilution significantly increased proliferation in VSMCs (571 ± 70%, $p < 0.001$). Osteopontin production was increased by 138 ± 0.03% ($p < 0.007$) in the presence of macrophage conditioned media (1:4) as compared to control media. Northern analysis with a porcine cDNA probe revealed expression of osteopontin mRNA after stimulation of the smooth

MONDAY POSTER